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Kim Vitray
Operations Manager

Subscribed and sworn to before me this 30th day of January, 2006.

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SYSTEM FOR REMOVAL OF SMALL AMOUNTS OF BODY FLUID

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The present invention falls in the field of analysis of body fluids to establish a diagnosis or to monitor the concentration of metabolic parameters, for example, blood glucose concentration.

The invention concerns a system for removal of small amounts of body fluid, comprising a drive unit with a receptacle to receive a disposable pricking unit, which has a holding area and a capillary structure connected to the holding area. The capillary structure has at least one capillary channel, as well as a point facing away from the receptacle for pricking into the skin. The capillary structure is open outward at least in one part of its longitudinal extent.

Systems for removal of body fluids are already known in the prior art in which the body fluid is accommodated in the disposable element. Blood sampling and analysis systems having a disposable unit with a capillary to receive the body fluid and to transport the body fluid to a detection area are known from the document EP 0 199 484. A further development of this concept is described in WO 97/42888. The arrangement described here is suitable, in particular, to accept relatively small amounts of body fluid, which occurs primarily by pressure of a ring on the area surrounding a removal site and a pump movement. A system for analysis based on small amounts of interstitial fluid is known from EP 0 723 418. For this purpose, a very thin, closed cannula is inserted into the dermis and interstitial fluid is conveyed through the cannula to a test zone by exerting a pressure on the area surrounding the insertion site. A highly miniaturized arrangement, which also operates with a closed cannula to receive the body fluid, is known from

US 5,801,057. A particular advantage of this arrangement consists of the extremely thin cannula, which can be inserted largely pain-free at least in the arm area of the patient.

Whereas the arrangement described in US 5,801,057 already satisfies a number of the requirements existing in practice, there are some properties still in need of improvement. A general problem underlying the sampling devices according to the aforementioned document is production of the employed cannulas cost effectively and as small as possible. During miniaturization. in particular, which is desirable in terms of least possible pricking pain and smallest possible pricking wound, high manufacturing costs for the very thin closed cannulas occur and there are essential feasibility problems.

According to the present invention, the requirements on systems for sampling of small amounts of body fluid are solved, in particular, by the fact that, instead of the closed cannula structures known in the prior art, cannulas with an open capillary structure are used. Not only are significant advantages in production gained by this, which make the sampling system more cost-effective and easier to produce, but major advantages in accommodating the body fluid are also obtained, since this can occur not only via the cannula tip, as in closed cannula structures, but also over the open area of the capillary structure. Moreover, the advantage that the open channel region of the needle is also capable of accommodating blood from the skin surface in the still inserted state and its transport to a detection zone can also be exploited.

Systems for removal of small amounts of body fluid find application especially in so-called spot monitoring, in which the concentration of specific analytes contained in body fluids is determined at a specific time. Such measurements can occur repeatedly at time intervals in order to monitor a change in analyte concentration. Such analysis, using disposable test elements, has proven to be very advantageous, especially in the field of blood sugar measurement of diabetics. If unduly high blood sugar values (hyperglycemia) occur in a diabetic over a certain period, this can result in serious long-term damage, like blindness and gangrene. On the other hand, if a diabetic enters a state of low blood sugar (hypoglycemia), for example, because he has injected an unduly large dose of insulin, this can be life threatening if the diabetic falls into so-called hypoglycemic shock. By regular monitoring of blood sugar levels, the diabetic, on the other hand, can avoid hyper- and hypoglycemic states and also learn over time how to adjust eating habits, physical activity and insulin medication to each other. In addition to improving or maintaining the health situation of diabetics, regular blood sugar monitoring also provides significant economic advantages, since high costs for subsequent diseases can be avoided. The reasons standing in the way of even further use and consistent application of blood sugar monitoring are primarily the pain for the necessary removal of the body fluid and the extensive handling steps in the systems widespread on the market. In the presently used systems diabetics or medical personnel must first obtain a drop of blood, which generally occurs on a fingertip. If

this is to occur as free of pain as possible, so-called pricking aids are used. A pricking aid must be initially equipped with a lancet, tightened, positioned on the body surface and triggered. After the pricking process the user must milk his finger and produce a drop of blood from the pricking wound, which should be as small as possible. Even before this procedure the diabetic must provide the blood sugar measurement device with a test strip and start it. The drop of blood can now be placed on the test strip and after, say, 10 sec, a measured blood sugar value is available. The user must now still dispose of the lancet and test strip employed. The present invention makes it possible to highly simplify the described blood sugar measurement process by providing a so-called integrated system in which pricking, sampling and the analytical reaction occur with the same (disposable) unit.

A system according to the present invention is used to sample small amounts of body fluid. Body fluids in this context are understood to mean blood, interstitial fluid and mixtures of these body fluids. Whereas in ordinary blood sampling systems this generally occurs in the fingertip, body fluids can also be taken at other locations of the body, for example, the forearm with the sampling system according to the invention.

A disposable pricking unit for removal of small amounts of body fluid according to the present invention has a holding area with which the proximal end of an elongated capillary structure is connected to at least one capillary channel for transport of the body fluid. The distal end of the capillary structure is suitable for pricking the skin and at least one part of the capillary structure is open outward along its longitudinal extent. Capillary structure in the context of the invention is understood to mean an object which, when brought in contact with body fluid in its distal region, transports it as a result of capillary forces in the direction of the proximal end of the capillary structure. In terms of this function the capillary structure according to the invention is similar to the hollow cannulas described in US 5,801,057 and EP 0 723 418. However, an essential difference is produced by the fact that at least one area, which includes at least part of the longitudinal extent of the capillary structure, opens outward. The longitudinal extent of the capillary structure extends from the proximal end, which is connected to the holding area, to the distal end, which is provided for pricking in the skin. The hollow cannulas of the prior art only have an opening on their outermost distal end, through which the body fluid can enter. In contrast to this, the capillary structure according to the invention can receive body fluid over a much larger part of its longitudinal extent. In the general case the length of the area of the capillary structure that is open outward is more than 10% of the longitudinal extent of the capillary structure, preferably more than 50% of the longitudinal extent. For reasons of manufacture it is particularly favorable if the capillary structure opens outward along its entire longitudinal extent.

Ordinary hollow cannulas are produced in the prior art by drawing out thicker tubes. It is apparent from this that production of very thin hollow cannulas, for example, with an outside

diameter below 0.3 mm, is very demanding and costly. On the other hand, a different method is described in US 5,801,057. A first element is etched from silicon, which has a needle area with a groove and a measurement chamber integrally connected to the needle. The measurement chamber and groove in the needle area are then closed with a layer. Connection of the two elements is achieved, for example, by anodic bonding. Significant manufacturing costs are incurred in terms of high miniaturization of the blood sampling device and the bonding process step. The arrangement so produced, corresponding to the document of the prior art already mentioned, also can only receive liquid through the tip region of the needle. It was found according to the invention that it is possible to also achieve efficient acceptance of fluid, if an open capillary is present. Examples of such open capillaries are described below:

Open capillaries can be produced in similar fashion to the document US 5,801,057 by a photolithography method, as is known from the field of semiconductor technology. It is also possible to provide solid needles with channels, grooves or the like that open outward by milling, etching, etc. Such recesses lead from the tip, at least a region adjacent to the tip, to the proximal end of the needle, which is connected to the receptacle. These recesses or capillaries need not necessarily be straight, but can also be coiled, meandering or the like. It is significant that liquid is transported by the capillary from the distal area of the needle into the proximal area. The cross section of the capillary can be V-shaped, semicircular or also rectangular. It is critical that part of the cross section opens outward so that fluid can penetrate into the capillary channel over the outside peripheral surface of the needle.

In addition to the already mentioned possibilities of introducing capillary channels in rod-like elements, it is also possible to generate the capillary channels by joining of elements. For example, it is possible to fasten two or more solid needles to each other, for example, weld them together so that capillary channels are formed by the contact areas of the solid needles. It is also possible to twist wires in the form of a strand together so that a number of contact areas that generate capillary channels are formed.

The capillary channels that are present in the capillary structure are typically deeper than they are wide. The ratio of depth to width (generally referred to as aspect ratio) is advantageously from 2 to 5. The cross section of the capillary channel is typically larger than 2500 μm^2 and smaller than 1 mm^2. As already mentioned above, it is favorable that the capillary channels are accessible from the outside so that body fluid can also be accommodated in them while the capillary structure is inserted into tissue. In order to achieve good accommodation of the body fluid, the area of the capillary structure opened outward should have a length of 1 mm or more.

The holding area is connected to the proximal part of the capillary structure. The holding area and capillary structure can be designed both in one piece (monolithic) and as separate parts, which are joined by gluing, melting, force-fitting, etc. Monolithic structures can be produced

particularly favorably from semiconductors with the production methods known for semiconductors. Very high miniaturization can be achieved on this account. Production of the pricking unit from a separate holding area and a separate capillary structure, on the other hand, can be more favorable in terms of manufacturing costs. A pricking device made of separate elements can be formed, for example, from a metal capillary structure and a plastic holding area.

A pricking unit according to the invention can have an evaluation zone in the proximal area of the capillary structure or in the holding area. If an evaluation of the analyte concentration is conducted, for example, by infrared spectroscopy, the detection zone does not have to contain any additional reagents that permit determination of the analyte. Since the materials for the capillary structure and the holding area are generally not transparent to infrared, a reflection spectroscopic analysis is preferred. For this purpose the evaluation zone is preferably IR reflective, which is sufficiently present in metal surfaces in general. Plastics could be made IR reflective by evaporation of sputtering of gold or aluminum (as an alternative, optically transparent windows can also be integrated).

In the preferred case the pricking unit, however, has a detection zone in which a reagent is arranged, which experiences a detectable change with an analyte being detected in the body fluid sample. Typical reagents for detection of glucose are based, for example, on glucose oxidase in conjunction with a color-producing redox system. Reagents that form a color with glucose from the body fluid for optical evaluation are adequately known from the prior art. Reagents that permit electrochemical detection of an analyte are also known from the field of blood sugar measurement strips. Since such detection systems are adequately known from the prior art, they will not be further described here.

The reagent systems mentioned can be arranged in the proximal area of the capillary structure, to be recorded and evaluated there, but because of the relatively unfavorable possibilities of the reagents, an arrangement of the reagents in the holding area is preferred. In order to permit wetting of the reagents with the body fluid, the reagent is either directly connected to the capillary structure and can absorb the body fluid through its own capillary forces or a fluid connection is provided (for example, a connection channel, Flies [sic; probably a typo for "flow"], etc.) provided from the capillary structure and the detection zone, through which the body fluid can reach the detection zone from the capillary structure. The pricking unit can be designed so that a capillary channel of the capillary structure is brought into the holding area and a reagent is applied directly to the capillary channel passing through the holding area. The reagent mixtures employed are normally solid and because of their ingredients (for example, aluminum oxide, kieselguhr, etc.) have such high capillarity that they can absorb the body fluid from the capillary channel.

The shape of the holding area is relatively noncritical. For example, it can have the shape of a small cuboid, which has a recess to receive the reagent mixture. For fastening of the pricking unit in a drive unit no special expedients are generally necessary and configurations known for disposable lancets of ordinary blood sampling systems can be resorted to. For example, the holding area can have taperings into which spring elements of a receptacle of a drive unit engage in order to hold the pricking unit. The pricking unit is advantageously positioned within the receptacle (for example, by pressing of a side facing away from the tip of the pricking unit against a stop) so that good control of the pricking depth of the pricking unit can be guaranteed. For such mounting and cooperation of the receptable and disposable pricking unit, document EP B 0 565 970 is referred to.

A detection unit can advantageously be integrated in the system for sampling small amounts of body fluid. If a pricking unit is used with a reagent that undergoes a color change or color formation in the presence of an analyte, the system can have an optical detection unit comprising a light source and a detector for detection of transmitted or reflected light. When electrochemical detection is used, the system can have electrodes that contact the reagent of the pricking unit or the contacts of the pricking unit which in turn contact the reagent. For evaluation the system can have the electronic devices known in the prior art in order to determine the concentration of analyte, for example by measurement of the so-called Cotrell [sic; Cottrell] current. For a case in which a reagent-free analysis is to be conducted, the system can include, for example, an infrared radiation source and an infrared detector, as well as the devices for spectral resolution of the reflected radiation of the evaluation zone.

The sampling system according to the invention also has a drive unit, which moves the receptacle on activation from a first to a second position so that the pricking unit executes a pricking motion. Such drive units are adequately known from the field of blood sampling systems. They can include, for example, a spring, which is tightened by the user and drives the pricking unit when released. A particularly advantageous drive unit is described in EP B 0 565 970.

With the pricking unit according to the invention and the sampling system according to the invention, sampling of body fluid can occur while the capillary structure or part of it has been inserted into the skin (i.e., removal directly from the body or removal of fluid emerging from the body on the body surface) or the capillary structure can be withdrawn from the body after a prick is made and body fluid emerging from the body surface absorbed. Sampling in which the capillary structure remains in the body for absorption of the body fluid, is particularly suitable for sampling on the arm. This is due to the fact that small prick wounds on the arm reclose very quickly so that no or only very small amounts of fluid emerge after the prick. On the other hand, the sensation of pain on the arm is less pronounced than, say, on the finger, so that leaving the

capillary structure in the body is not perceived as painful. As already mentioned above, an outward open capillary structure has the advantage over ordinary hollow cannulas that fluid can be taken up over the open region, whereas the area of liquid absorption in hollow cannulas is restricted merely to the front end of the cannula. The latter is particularly disadvantageous if the needle opening during pricking is closed by tissue parts so that no fluid or insufficient fluid can be absorbed.

During sampling in which the capillary structure is withdrawn from the tissue after the pricking process, this also has an advantage over the ordinary hollow cannulas. As already mentioned, outward open capillary structures can be produced more simply and cost-effectively than closed hollow cannulas,

A sampling process that is a combination of the aforementioned methods can also be carried out with the pricking units according to the invention. In this combination method pricking is initially carried out, the capillary structure is partly withdrawn from the pricking zone and allowed to stay there for a few seconds for a collection period. This method has the advantage that part of the pricking channel is exposed by withdrawing the capillary structure so that the body fluid can collect in it and penetrate the capillary structure from there.

Another critical factor that is important for efficient collection of body fluid by means of the capillary structure is the wettability of the capillary channels. If capillary structures made of silicon are used, these are generally sufficiently wettable through a silicon oxide layer on the surface. If metals are used for the capillary structure, these are often relatively poorly wettable. However, this can be countered by a number of appropriate measures, for example, by silicate coating of the surface. Sufficiently high wettability is generally produced if the fluid in the capillaries has a concave meniscus, which is equivalent to having a wetting angle smaller than 90°.

The invention is further explained by means of figures:

Figure 1: Disposable pricking unit made of silicon.

Figure 2: System for sampling of body fluid comprising the pricking unit from Figure 1 and a drive unit, as well as an optical evaluation device.

Figure 3: Capillary area of a disposable pricking unit formed from two solid needles welded together.

Figure 4: Capillary structure formed from wires twisted together (strand structure).

Figure 5: Capillary structure in the form of a solid needle on whose surface capillary channels are found.

Figure 1 shows a disposable pricking unit in three views. It is apparent from the perspective view in Figure 1A that the pricking unit 10 has a capillary structure 11 arranged in a holding area 12. The holding area 12 is covered with a plate 13 having a window 14. The

capillary structure 11 is designed so that it has a point on its distal end in order to penetrate the skin. A capillary channel 15 is also arranged in the capillary structure, which opens upward. This capillary channel runs in the interior of the pricking unit and reaches a detection zone arranged beneath window 14. The end 15A of the capillary channel in the window area is apparent in Figure 1B. The end is visible in this case, since no test chemistry is arranged above the channel. In the use condition, however, a detection area is arranged above this end, for example, an optical detection system for glucose.

Figure 1C shows a side view of the pricking unit, from which it is apparent that the capillary channel 15 is open both upward and also laterally on the distal end of the capillary structure. The length of the depicted capillary structure is 1.6 mm and the width and depth of the capillary channel 15 are 50 and 150 µm.

Figure 2 shows a system (20) for sampling bold fluid which includes a pricking unit according to Figure 1 as well as a drive unit and an optical evaluation device. The figure shows a system based on a blood sampling device according to EP 1034740. The pricking unit according to Figure 1 is situated in the receptacle of the blood sampling device in which a disposable lancet is arranged in the previous systems. By operating the pushbutton 21 the drive mechanism is tightened and by operating the triggering button 22 the pricking process, i.e., movement of the pricking unit, is initiated. In this case the capillary area 11 emerges from an outlet opening (not shown) of cap 23 (shown with a dashed line) and punctures the skin, which is situated at the cap opening for blood sampling. In contrast to the blood lancet devices, which are available commercially under the name Softclix Pro, however, the capillary area is not retracted behind the cap opening but remains with its maximum pricking depth in the tissue or is partially withdrawn so that removal of the emerging body fluid in the capillary is possible. As outlined in conjunction with Figure 1, body fluid reaches an evaluation area through the capillary in which an analyte determination is possible. An optical evaluation is shown in Figure 2, which includes a light source 24 as well as a photodetector 25. The window 14 of the evaluation area is illuminated by light source 24 (for example, light-emitting diode) and radiation reflected from the evaluation area is picked up with photodetector 25. With an evaluation unit (not shown) arranged in the system, an analyte concentration is determined from the intensity received with the photodetector and displayed on display 26. After the measurement is complete the user can remove system 20 from the body surface, take off cap 23 and dispose of pricking unit 10. For another measurement a new pricking unit, for example, from a magazine, can be placed in receptacle 27 of the system.

Figure 3 shows the generation of the capillary structure by welding two solid needles. It is apparent in Figure 3 that by welding two cylindrical metal wires in the connection area two opposite capillary channels are formed which are opened outward. The structure obtained is ground on one end in order to form a point, which permits pricking in the skin. In the example

depicted, metal wires from medical stainless steel with a cross section of 400 µm were used. The tip area 11a of the capillary structure has a length of about 2 mm. Welding of the two wires occurred by passing current through the two wires, in which one wire was connected as anode and the other wire as cathode.

Figure 4 shows a capillary structure in the form of a strand. To generate this strand structure 40, metal wires with a diameter from 20 to 70 µm were twisted together and cut obliquely on one end so that a point area 40a was produced, which can be inserted into the skin. The cutout enlargement in Figure 4, which shows the point area, shows the open capillary channels (marked by arrows) that form from the wires lying next to each other.

Figure 5 shows a capillary structure 50 generated from a solid needle. The needle has a proximal area 50b, which can be mounted in a holding area. The point area 50a of the needle is ground as in conventional blood lancets in order to permit simple, painless penetration into the skin. A capillary channel 51 was made in the solid needle by milling, which is open outward. The cross section of this capillary channel is about 60 × 150 µm.

Claims

1. System for sampling of small amounts of body fluid with a drive unit, having a receptacle which, on activation of the drive unit, moves from a first to a second position, as well as with a disposable pricking unit which has a holding area arranged removable in the receptacle, the proximal end of an elongated capillary structure with at least one capillary channel for transport of the body fluid is connected to the holding area and the distal end of the capillary structure is suitable for pricking of the skin, in which the distal end of the capillary structure is situated outside of the skin when the receptacle is arranged in the first position, and in the second position has penetrated the skin to the pricking depth, characterized in that the at least one capillary opens outward in an area that includes at least part of the longitudinal extent of the capillary structure.

2. System according to Claim 1, in which the entire length of the capillary structure from the proximal to the distal end opens outward.

3. System according to Claim 1, in which the holding area has a detection zone for detection of one or more analytes, in which the detection zone is arranged so that the body fluid can be taken up by the capillary structure.

4. System according to Claim 1, in which the drive unit moves the pricking unit so that it stops in the second position for a time interval (collection period) and the pricking unit is then moved to a position in which the distal end of the capillary structure is situated outside of the skin.

5. System according to Claim 1, in which the drive unit moves the pricking unit so that after it reaches the second position it is moved back to a collection position in which the part of the capillary structure situated in the skin is shorter than in the second position.

6. System according to Claim 1, in which the capillary structure and holding area are integrally connected to each other.

7. System according to Claim 1 or 6, in which the holding area and capillary structure are made from a semiconductor, preferably silicon.

8. System according to Claim 6 or 7, in which the holding area and capillary structure are produced integrally from a single material part.

9. System according to Claim 1, in which the outward open area of the capillary structure has the form of a channel.

10. System according to Claim 9, in which the channel-like area has an essentially V-shaped cross section.

11. System according to Claim 1, in which the length of the capillary structure lies in the range from 0.3 to 3 mm and the cross section of the capillary structure in the range from 0.03 to 0.8 mm.

12. Disposable pricking unit for removal of small amounts of body fluid, having a holding area with which the proximal end of an elongated capillary structure is connected to at least one capillary channel for transport of the body fluid and the distal end of the capillary structure is suitable for pricking the skin, characterized in that the at least one capillary channel is open outward in an area that includes at least part of the longitudinal extent of the capillary structure.

Summary

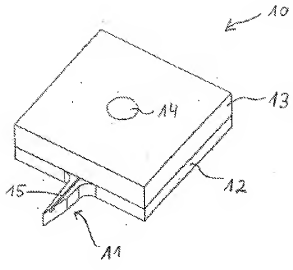
System for removal of small amounts of body fluid with a drive unit, which has a receptacle, which on activation of the drive unit is moved from a first or second position, as well as with a disposable pricking unit, which has a holding area that is arranged removable in the receptacle, with which holding area the proximal end of an elongated capillary structure (grammar?*) is connected to at least one capillary channel for transport of the body fluid and the distal end of the capillary structure is suitable for pricking of the skin, in which the distal end of the capillary structure, when the receptacles arranged in the first position, is situated outside the skin and in the second position has penetrated the skin to a depth, the pricking depth, characterized by the fact that the at least one capillary channel is open outward in an area that includes at least part of the longitudinal extent of the capillary structure.

[Translator's Note: Comment in the source document apparently calling attention to the mistake made in this sentence. "Holding area" should have been omitted.]

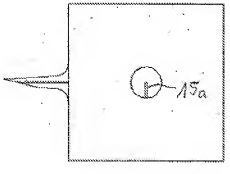
Disposable pricking unit for removal of small amounts of body fluid, having a holding area with which the proximal end of an elongated capillary structure is connected to at least one capillary channel for transport of body fluid and the distal end of the capillary structure is suitable for pricking the skin, characterized by the fact that the at least one capillary channel is open outward in a region that includes at least part of the longitudinal extent of the capillary structure.

Fig. 1

A



B



C

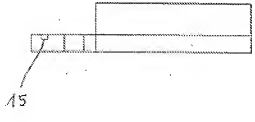


Fig 2

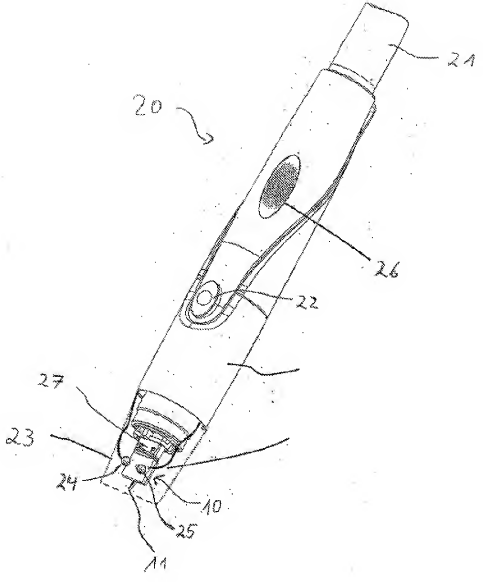


Fig. 3

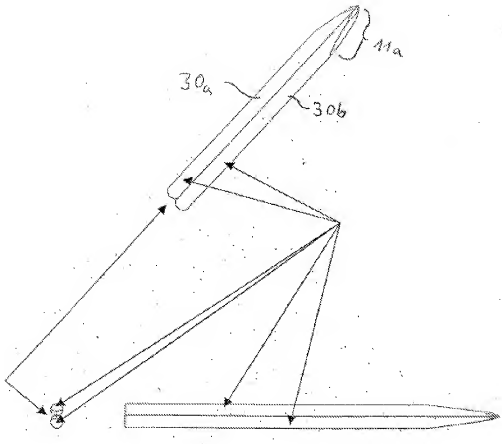


Fig 4

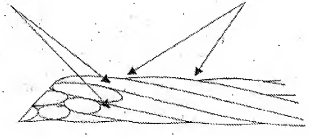


Fig 5